*METHADONE

Class: Opioid analgesic.

Indications: Severe pain, cough, †an alternative in cases of intolerance to other strong opioids, †**morphine** poorly-responsive pain, †pain relief in severe renal failure.[1,2]

Pharmacology

Methadone is a synthetic strong opioid with mixed properties.[3,4] Thus, it is a μ-opioid receptor agonist, possibly a δ-opioid receptor agonist,[5] an NMDA-receptor-channel blocker,[6,7] and a presynaptic blocker of serotonin re-uptake.[8] Methadone is a racemic mixture; L-methadone is responsible for most of the analgesic effect, whereas D-methadone is antitussive. Methadone is a non-acidic and lipophilic drug which is absorbed well from all routes of administration. There is a high volume of distribution with only about 1% of the drug in the blood. Methadone accumulates in tissues when given repeatedly, creating an extensive reservoir.[9] Protein binding (principally to a glycoprotein) is 60–90%;[10] this is double that of **morphine**. Both volume of distribution and protein binding contribute to the long plasma halflife, and cumulation is a potential problem. Methadone is metabolized chiefly in the liver to several metabolites.[11] About half of the drug and its metabolites are excreted by the intestines and half by the kidneys, most of the latter unchanged.[12] Renal and hepatic impairment do not affect methadone clearance.[13, 14]

In single doses, methadone PO is about 1/2 as potent as IM,[15] and IM a single dose of methadone is marginally more potent than **morphine**. With repeated doses, methadone is several times more potent and longer acting; analgesia lasts 8–12h and sometimes more. There is no single potency ratio for methadone and **morphine**, and the eventual 24h dose of methadone *is typically 5–10 times smaller than the previous dose of **morphine**, sometimes 20–30 times smaller, and occasionally even smaller.*[16-18] The potency ratio tends to increase as the dose of **morphine** increases, i.e. proportionately less methadone is required as the **morphine** dose increases.[16, 19]

Methadone is used in several different settings, guided mainly by clinical experience. A systematic review of methadone for cancer pain identified eight RCTs but, because different methods were used, meta-analysis was not possible.[20] First-line, methadone provides similar analgesia to **morphine** but more undesirable effects. In a double-blind study, 20% of patients commenced on methadone (7.5mg b.d.) vs. 5% on **morphine** (15mg b.d.) discontinued treatment, mainly due to sedation or nausea, with half of the withdrawals occurring in the first week.[21] This suggests that a smaller starting dose of methadone (i.e. 2.5–5mg b.d.) is more appropriate. Second–line, patients who experience inadequate analgesia with **morphine**, with or without unacceptable undesirable effects such as nausea, vomiting, hallucinations or sedation, can obtain good relief with relatively low-dose methadone with few undesirable effects.[16,18,22] Patients who experience more specific neurotoxicity with **morphine**, e.g. hyperalgesia, allodynia and/or myoclonus ± sedation and delirium, generally also benefit by switching to methadone. However, switching to other opioids, e.g. **fentanyl**, **oxycodone**, also helps.[23-25] Accordingly, it would seem logical, when switching from **morphine**, to choose an opioid which is easier and safer to use than methadone, such as **oxycodone**, **hydromorphone** or **fentanyl**.

Methadone is an alternative strong opioid for patients with chronic renal failure who would also be at risk of excessive drowsiness ± delirium with **morphine** because of cumulation of morphine-6-glucuronide.[2] Methadone is poorly removed by hemodialysis.[26] However, for moribund patients, **alfentanil** is probably a better choice (see Opioids in renal impairment, p.000). Methadone can also be used as a strong opioid analgesic in former narcotic addicts who are being maintained on methadone.[27]

Bio-availability 80% (range 40–100%) PO.
Onset of action <30min PO[28]; 15min IM.
Time to peak plasma concentration 4h PO; 1h IM.
Plasma halflife 8–75h;[29] longer in older patients; acidifying the urine results in a shorter halflife (20h) and raising the pH with sodium bicarbonate a longer halflife (>40h).[30]
Duration of action 4–5h PO and 3–5h IM single dose; 8–12h repeated doses.

Cautions

The lipid-solubility and long halflife of methadone means that cumulation to a significant extent is bound to occur, particularly in elderly patients; p.r.n. dose titration is generally necessary to avoid this hazard (see below).[31]

Methadone is principally metabolized by CYP3A4; CYP2D6, 2C9, 2C19 and 1A2 may play minor roles. MAOIs may prolong and enhance the respiratory depressant effects of methadone. **Carbamazepine**, **phenobarbital**, **phenytoin** and **rifampin** increase the metabolism of methadone; **amitriptyline**, **cimetidine**, **ciprofloxacin**, **fluconazole** and SSRIs decrease its metabolism. Methadone increases plasma **zidovudine** concentration. **Efavirenz**, **lopinavir-ritonavir**, **nelfinavir**, **nevirapine** and **ritonavir** (all antiretroviral agents) may reduce plasma methadone concentrations.

Undesirable effects
For full list, see manufacturer's PI.
Local erythema and induration when given by CSCI.[32] Rarely, methadone may cause neurotoxicity, e.g. myoclonus.[33] Prolonged QT interval (dose related; of uncertain clinical significance).[34-36] (See also Strong opioids, p.000.)

Dose and use
Dose titration is different from **morphine** because of the wide inter-individual variation in the pharmacokinetics of methadone. Several guidelines exist for switching from **morphine** to methadone, but all require practitioners to be experienced in the use of methadone and close observation of the patient, generally as an inpatient.[2,16-18,22,37-41] Some have reported carefully controlled outpatient regimens, but pain relief can take weeks rather than days to achieve.[38,41] When using methadone, the implication of its large volume of distribution must be considered. During the first few days, while the body tissues become saturated, a greater daily dose of methadone will be required for satisfactory analgesia than subsequently; once saturation is complete, a smaller daily dose of methadone is then sufficient. Continuing on the initial daily dose is likely to result in sedation, respiratory depression, and even death.[42]

PCFusa favors a 'stop and go' approach, i.e. the abrupt cessation of the **morphine** and introduction of methadone p.r.n. (see guidelines, p.000). These guidelines are an evolution from earlier ones, incorporating feedback to palliativedrugs.com from clinicians.[2,17] A single loading dose aids tissue saturation and helps to reduce the number of p.r.n. doses required in the first 48h.[17] The recommendations may be overcautious but are safer, particularly in the elderly and for those switching from large doses of **morphine**.

Several other methods for switching from morphine or from another strong opioid have been published.[40,43-46] Regardless of the method used, the importance of close supervision cannot be over-emphasised. Maintenance doses vary considerably, but most are <80mg/24h.[39] *Subsequent switching from methadone to other opioids can be difficult. In one series 12/13 patients experienced increased pain ± dysphoria*.[47]

Methadone by CSCI often causes marked local inflammation necessitating site rotation, and possibly other measures (see guidelines, p.000).[48] Methadone can also be given PR, IV, CIVI ± PCA.[45,49-51] It has also been used as an effective mouthwash for painful mouth ulcers.[52]

Supply

Unless indicated otherwise, all preparations are **schedule II** controlled substances.

Methadone (generic)
Tablets 5mg, 10mg, 40mg, 28 days @ 30mg b.i.d. = $???.
Oral solution 5mg/5ml, 10mg/5ml, 28 days @ 30mg b.i.d. = $???.
Oral concentrate 10mg/ml, 28 days @ 30mg b.i.d. = $???.
Injection 10mg/ml, 20ml amp/vial? = $???.
Powder for compounding 50g, 100g, 500g = $???, ??? and ??? respectively.

Dolophine® (Roxane)
Tablets 40mg, 28 days @ 40mg b.i.d. = $???

Methadose® (Mallinckrodt)
Tablets 5mg, 10mg, 28 days @ 30mg b.i.d. = $???

GUIDELINES FOR THE USE OF METHADONE FOR CANCER PAIN

Caution: Therapeutic inequivalence
Methadone has both opioid and non-opioid properties, and a long variable halflife (approximately 8–80h vs. 2.5h for morphine). There is therefore no single potency ratio for methadone and other opioids. When switching from morphine, the eventual 24h dose of methadone is typically 5–10 times smaller than the previous dose of morphine, and can be much smaller. Inevitable cumulation is the reason for the week-long intervals between adjustments in the regular dose. Switching to methadone must be closely supervised, normally as an inpatient. If in doubt, seek specialist advice.

Indications for use

Methadone is used in various situations, including:

- neuropathic or mixed nociceptive-neuropathic cancer pain not responding to an NSAID + morphine + adjuvant analgesics, e.g. an antidepressant ± an anti-epileptic
- neurotoxicity with morphine at any dose (e.g. myoclonus, allodynia, hyperalgesia) which does not respond to a reduction in morphine dose
- the strong opioid of choice, instead of morphine
- end-stage renal failure.

Dose titration

1. When prescribing methadone PO as first-choice strong opioid:
   - start with methadone 5mg q12h regularly and 5mg q3h p.r.n.; 2.5mg in the elderly
   - if necessary, titrate the regular dose upwards once a week, guided by p.r.n. use during the last 2 days
   - continue with 5mg p.r.n., or 2.5mg in the elderly
   - with doses ≥30mg q12h, increase the p.r.n. dose to 1/4 of the q12h dose.
2. If the patient is already receiving morphine, use the method described below.
3. If using another strong opioid, convert to the morphine equivalent daily dose and then follow the guidelines for morphine.
4. If converting from methadone PO to methadone SC/IV, or from another opioid CSCI/CIVI, see the respective boxes below.
5. For patients in severe pain unable to wait 3h before giving the next dose, options include:
   - taking the previously used opioid q1h p.r.n. (50–100% of the p.r.n. dose used before switching)
   - if neurotoxicity with the pre-switch opioid, use an alternative strong opioid.
6. The switch to methadone is successful (i.e. improved pain relief and/or reduced toxicity) in about 75% of patients. Occasionally, a patient:
   - becomes over-sedated → reduce the dose (some centers monitor the level of consciousness and respirations q4h for 24h)
   - develops opioid withdrawal phenomena; give p.r.n. doses of the previous opioid to control these.

Morphine PO to methadone PO

Morphine is stopped abruptly when methadone is started.

If switching from:

- normal release morphine, give the first dose of methadone ≥2h after last dose of morphine
- SR morphine, give the first dose of methadone ≥6h after the last dose of a 12h preparation, or ≥12h after the last dose of a 24h preparation.

Give a single loading dose of PO methadone 1/10 of the previous 24h PO morphine dose, up to a maximum of 30mg.

Give q3h p.r.n. doses of methadone 1/30 of the previous 24h PO morphine dose, up to a maximum of 30mg per dose.

On Day 6, the amount of methadone taken over the previous 2 days is noted and divided by 4 to give a regular q12h dose, with 1/4 of the regular q12h dose q3h p.r.n.

If ≥2 doses/day of p.r.n. methadone continue to be needed, the dose of regular methadone should be increased once a week, guided by p.r.n. use.

Methadone PO to methadone SC/IV and CSCI/CIVI

Due to its long halflife, methadone (10mg/ml) can be given SC q12h, but if SC injection is painful or causes local inflammation, give by CSCI/CIVI instead.

To convert from PO methadone to methadone SC/IV, halve the PO dose.

For patients in severe pain unable to wait 3h before giving the next dose, options include:

- the previously used opioid q1h p.r.n. (50–100% of the p.r.n. dose used before switching)
- if neurotoxicity with previous opioid, use an alternative strong opioid.

If CSCI methadone causes a skin reaction:

- administer as a more dilute solution in a 20ml or 30ml syringe
- change the syringe q12h and the site daily.

For additional rescue doses of methadone SC/IV, give 1/10 of the 24h CSCI/CIVI dose q3h p.r.n. If ≥2 p.r.n. doses/day continue to be needed, the methadone 24h CSCI/CIVI dose should be increased by 1/4–1/3 once a week.

Other opioids CSCI/CIVI to methadone CSCI/CIVI

The safest approach is to follow the method for PO switching, using bolus injections of methadone SC/IV instead of PO doses.

Convert the opioid 24h CSCI/CIVI dose to its PO equivalent and determine the methadone PO dose (Dose titration, point 2).

The SC/IV dose of methadone is half the PO dose; the maximum initial dose of methadone SC/IV will be 15mg.

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